Review Article

Role of Hyperhomocysteinemia and Hyperuricemia in Pathogenesis of Atherosclerosis

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Background: The mechanisms of hyperhomocysteinemia (HHcy) and hyperuricemia (HUA) that promote atherosclerosis were seldom explored and always indefinite. Therefore, we will discuss some new reviews about the role of HHcy and HUA in the pathogenesis of atherosclerosis. *Methods:* This study was conducted by reading a lot of literature, including basic research and clinical application research. *Results:* HHcy is known as an independent risk factor for atherosclerosis. Possible mechanisms for the association between homocysteine and atherosclerosis include stimulating smooth muscle cell growth, reducing endothelial cell growth and endothelial cell relaxation, and decreasing synthesis of high-density lipoprotein. HUA causes endothelial dysfunction and thereby increases oxidative stress, inducing vascular smooth muscle cell proliferation and reducing endothelial nitric oxide bioavailability. HUA plays a role in the development and pathogenesis of metabolic syndrome, hypertension, stroke, and atherosclerosis. *Conclusions:* Accelerated atherosclerosis may be a consequence of the combined effect of HHcy and HUA. **Key Words:** Hyperhomocysteinemia—hyperuricemia—atherosclerosis—mechanisms.

Introduction

Hyperhomocysteinemia (HHcy) is typically defined as levels >10^{-2}mol/L in reported studies.[1] The first involvement of HHcy in atherosclerosis was made by McCully approximately 40 years ago, which is based on pathological findings in infants with HHcy resulting from inborn metabolism deficiency.[2] A large number of epidemiological studies suggest that increased homocysteine level is an independent risk factor for vascular diseases, including stroke.[3,4] HHcy-induced oxidative stress, endothelium dysfunction, inflammation, smooth muscle cell proliferation, and endoplasmic reticulum (ER) stress have been considered to play an important role in the pathogenesis of atherosclerosis.

Uric acid, the end product of purine catabolism in humans, is known as an antioxidant. Several studies suggest serum uric acid levels have an association with surrogate markers of atherosclerosis. In particular, there is evidence that hyperuricemia (HUA) has an independent effect on atherosclerosis, which has a direct effect on key processes involved in endothelium function and vascular remodeling.[5] HUA is defined as greater than 7.0 mg/dL for men and greater than 5.6 mg/dL for women.[6] HUA is currently suggested to significantly modulate the physiological functions of various cells, particularly vessel endothelium, which

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may mediate these effects by inducing oxidative stress, endothelial dysfunction (ED), and inflammation.

Hyperhomocysteinemia and Atherosclerosis

Homocysteine is a thiol-containing amino acid derived from dietary methionine. Dietary methionine is converted to the methyl donor S-adenosylmethionine and is demethylated to S-adenosylhomocysteine and homocysteine.

HHcy and Oxidative Stress

It has been suggested that oxidative stress is the primary biochemical mechanism responsible for HHcy-induced cellular injury and dysfunction. Reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide, and hydroxyl radical, are produced during the auto-oxidation of homocysteine. The auto-oxidation of HHcy could be one of the sources of ROS production. In vivo,[7,8] HHcy also decreased bioavailability of nitrogen (NO), resulting in ED. In addition, decreased bioavailability of NO also contributes to thrombosis and atherosclerosis because endothelium-derived NO inhibits platelet aggregation and leukocyte adhesion. Although there is convincing research supporting the results that HHcy-mediated radical production elucidates the pathology of vascular injury, studies have not been able to completely underlie the exact mechanisms linking HHcy, oxidative stress, and cellular or tissue damage. Although there is no direct method to measure oxidative stress in humans, indirect estimates support the belief that ROS-mediated damage is via underlying molecular mechanism of HHcy-mediated vascular dysfunction. The inability of the tissue to scavenge harmful oxidants causes lipid peroxidation, protein modifications, endothelial damage, decreasing ability to synthesize NO, limited normal vasodilation, cell death, and alterations in tissue morphology.[8] It will be important for patients with HHcy to develop specific therapeutic strategies and approaches to treat or regulate oxidative-mediated vascular dysfunction. There are no data proving whether vascular dysfunction in human subjects with HHcy is improved with antioxidant therapy currently.

HHcy and Endothelial Dysfunction

HHcy-generated reactive oxygen and nitrogen species evoke damaging molecular effects that underlie vascular dysfunction. HHcy induces ED by altering virtually every component of NO metabolism, including NOS expression, localization, activation, and activity. Most studies point to Hcy-induced oxidative stress as the important mediator in this process, and treating endothelial cells (ECs) with pathophysiological concentrations of HHcy significantly decreases endothelial nitric oxide synthase (eNOS) protein expression in a dose-dependent manner.[8] HHcy has been shown to mediate changes in substrate and cofactor availability and binding that can disrupt NO synthesis. Initially, ECs can increase the synthesis and release of NO for defending themselves and detoxify HHcy, which in turn leads to the formation of S-nitrosohomocysteine, a potent vasodilator. Nevertheless, this defense mechanism is limited, and chronic exposure to HHcy ultimately causes impaired basal NO production, radical formation, and subsequent endothelial injury. HHcy can also decrease the bioavailability and bioactivity of NO by the oxidative degradation of NO forming $ONOO^-$.[9] This explains the observation of a decrease in NO detection as a result of limited bioavailability rather than suppressed production. The formation of both S-nitrosohomocysteine and $ONOO^-$ modulate vessel function by reducing the amount of active NO availability.

HHcy and Inflammation

Atherosclerosis is a chronic inflammatory disease; HHcy can promote inflammation.[10] In vitro studies have suggested that HHcy induces several proinflammatory cytokines production. HHcy has also been shown to increase expression of monocyte chemotactic protein 1 and interleukin-8 (IL-8) in cultured ECs, which is known to enhance monocyte attachment to the endothelium and their recruitment to the subendothelial cell space, a critical step in atherosclerotic lesion development.[11] Through the activation of nuclear factor kappa B (NF-κB), a transcription factor known to stimulate the production of cytokines, chemokines, leukocyte adhesion molecules, and hemopoietic growth factors, all of which are thought to lead to vascular inflammation and atherogenesis.[12] A study by Zhang et al[13] provides the first evidence demonstrating that severe HHcy induces systematic inflammation and accelerates atherosclerosis in a novel model of severe HHcy and hypercholesterolemia, which suggest that HHcy induces inflammatory monocyte subset differentiation in mice independent of hyperlipidemia, and in cultured splenocytes mostly via nicotinamide adenine dinucleotide two nucleoside phosphate oxidase-mediated oxidant stress, and indicate that HHcy-induced inflammatory monocyte subset differentiation may be responsible for the increased risk of cardiovascular and cerebrovascular diseases in HHcy. Studies have found that HHcy promotes the activity of NF-κB by reducing NF-κB protein nitrosylation, then stimulates the release of inflammation factor such as tumor necrosis factor-α, interleukin-8, and aggravates the inflammatory response.[14]

HHcy and Smooth Muscle Cell Proliferation

Proliferation of vascular smooth muscle cells (VSMC) is a prominent characteristic of atherosclerosis. HHcy can significantly promote the proliferation of VSMC by promoting the expression of adhesion molecules, chemokine, and the VSMC mitogen.[15] Physiological and pathological vascular remodeling involves the breakdown and synthesis of the extracellular matrix, which is initiated by a